REMARKS

Finality of the Office Action

Inasmuch as the Office Action mailed December 10, 2008 is a first Office Action on the merits following Applicants' submission with the request for continued examination (RCE) filed September 12, 2008, and the USPTO Patent Application Information Retrieval (PAIR) correctly identifying the outstanding Office Action as a non-final Office Action, it is submitted that the Examiner's contention regarding finality of the Office Action at page 11 is *incorrect.*

In a telephonic message, Applicants have informed the Examiner about the inconsistency between the status of the application in the "Office Action Summary" and page 11 of the Office Action. Favorable action is earnestly solicited.

Claims

Claims 1–4, 6, 7, 10 and 12–16 are under examination. Claims 5, 8, 9, 11, 17 and 18 are cancelled hereby without prejudice or disclaimer. Applicants reserve the right to reintroduce cancelled subject matter at any stage during prosecution.

Claims 19–25 are added by this paper.

Claim amendments

Claims 13 and 14 are recited as independent claims. Claims 15 and 16 are made dependent on claims 13 and 14, respectively.

New claims 19 and 20 are supported by, for example, original claim 6.

New claims 21 and 22 are supported by the disclosure contained in, for example, paragraph [0108] of the published US application having the serial No. 2004-0058975.

New claims 23 and 24 are supported by, for example, original claim 7.

New claim 25 is supported by, for example, original claim 11.

It is respectfully submitted that the claim amendments do not add new matter. Entry thereof is respectfully requested.

Exhibit

In the Exhibit enclosed herewith, the pharmacological effect of yet another EP_2 antagonist (ZKxxxx888) in combination with rofecoxib is shown.

Rejections under 35 U.S.C. §112,¶1

Claims 1, 3–11 and 13–18 are rejected under §112, ¶1 as allegedly being failing to provide

enablement. This rejection is respectfully traversed.

The basis for this rejection is stated at page 2 of the outstanding Office Action, wherein it is alleged that "the specification, while being enabling for antagonizing the EP_2 receptors by EP2 antagonists, does not provide enablement for other antagonizing methods." However, the Office Action does not provide any evidence to support this contention. It is now well-settled that the Patent Office needs to demonstrate evidence to doubt the objective truth of statements contained in Applicants' specification regarding enablement. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (Emphasis in original)

See also *In re Bundy*, 209 USPQ 48 (CPA 1981). Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. §112, first paragraph.

In the instant case, under one embodiment, the present claims are directed to methods for impairing cumulus expansion and oocyte maturation via antagonizing the EP_2 receptor and inhibiting cyclooxygenase Cox-2. Under a related embodiment, the claims are directed to methods for fertility control via antagonizing the EP_2 receptor and inhibiting cyclooxygenase Cox-2. The Office Action concedes that the present specification provides an enabling disclosure on EP2 receptor antagonists, such as, for example, AH6809 compound of claim 2. However, the Office Action proceeds to contend that "other antagonizing methods" are not enabled by the present specification. To this end, the Office Action fails to provide a single example of such non-enabled "other antagonizing methods." As such, in absence of objective evidence demonstrating otherwise, the Examiner's contentions are without legal merit.

As outlined in detail in the remarks section of the Reply filed September 12, 2008, Applicants submit that the rationale for the use of the claimed method(s) is clearly provided by the present specification. In light of this detailed disclosure, to assert a lack of enablement, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Patent Office has not presented any evidence to refute the findings or the conclusions made in the specification or the supporting publications. In addition, no evidence has been presented to support the contention that the claimed molecules could not be used, in a manner that is commensurate with

Applicants' claimed invention. The specification provides more than it needs, for example, that antagonism of the EP_2 receptor and inhibition of Cox-2 is useful in fertility control. To this end, Dr. Lindenthal's declaration filed September 12, 2008 and the experimental evidence therein further supports the disclosure in the specification. The data in the declaration provides experimental evidence that the Rofecoxib and ZK6073610 compounds of the present invention are useful in inhibiting the expansion of the cumulus oocyte complexes (COCs) *in vivo*. The declaration and the specification further teach that cumulus expansion is a prerequisite for ovulation and fertilization, and as such, the compounds of the present invention are useful in fertility control. In similar fashion, a skilled artisan, by performing the same or similar assays, can determine which compounds are useful for the claimed process without undue experimentation.

State of the art

In the paragraph bridging pages 6 and 7, the Examiner contends:

> The instant claims read on all modalities that would antagonize EP2 receptors, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Although various individual compounds possessing the disclosed EP2 receptors activity are known to those of skill in the art, no information is provided to guide the skilled artisan to those diverse genera of structurally divergent compounds possessing similar physiological activity. Examiner is unaware of any nexus, stated in the art, or herein disclosed, attributing the herein envisioned physiological activity to one, or another, structural formula. Simply stated the skilled artisan must employ experimentation to discover compounds possessing these EP2 antagonistic activities required to practice the claimed invention.

Applicants courteously submit that the Office Action fails to present any evidence to support the contention that any compounds within the genus of claimed molecules are non-enabled. In the absence of such evidence, the rejection is deficient under controlling case law. Moreover, decades of scientific studies, both at the basic and clinical levels, have established that receptor antagonism/inhibition can be elicited via various chemical/genetic approaches. To this end, the Examiner is cordially requested to review the supporting publications enclosed herein. The references unequivocally teach that routine chemical/genetic approaches, such as employing the AH6809 compound of the instant invention, can be used to provide EP2-antagonism. For example, peptide antagonists (i.e., another example of a chemical approach), single hairpin RNA (shRNA) against the transcript (i.e., genetic manipulation), antagonizing antibodies against EP_2 receptor, etc.

may be routinely employed. Moreover, these reagents and techniques for employing them were available to the skilled worker. See, Exhibit B, which is a product brochure of EP_2 inhibitors available via Santa Cruz Biotechnology Corp. The utility of indirect modulators, such as, for example, PGE-2 synthase inhibitors, are also known in the art. See, for example, Samuelson et al. (*Pharmacological Reviews*, 2007), a copy of which is enclosed herewith.

Working examples

In the paragraph bridging pages 4 and 5, the Examiner alleges:

> Applicant fails to set forth the criteria that structurally defines, or identifies, those compounds possessing EP2 antagonistic activity. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "EP2 antagonist" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define those structural classes of compounds required to practice the invention as herein claimed, as required by those guidelines set forth in *In re Wands*, supra. Absent exemplification providing guidance as to these compound classes herein envisioned, the instant specification fails to place those compound classes possessing various structural formulas requiring specific physiological EP2 antagonistic activity in the skilled artisan's possession, absent undue experimentation.

The Examiner's contention regarding the sufficiency of working examples is misplaced. There is no requirement that Applicant provide *any* working examples relating to the methods of use, such as, for example, inhibiting cumulus expansion or controlling fertility, to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502–503, 190 USPQ 214 (CCPA 1976). See, for example, *In re Howarth*, 654 F.2d 105, 210 USPQ 689 (CCPA 1981); and *In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA 1962). However, the disclosure provided in the instant specification provides clear guidance on how to employ the claimed compounds in, for example, inhibiting cumulus expansion and oocyte maturation. Moreover, in view of the experimental evidence discussed *supra*, the PTO's contentions are without merit. The utility of the molecules of the instant invention, for example, rofecoxib and ZK6073610, are fully described by the way of *in vitro* and *in vivo* models that utilize appropriate controls. In the Exhibit enclosed herewith, the pharmacological effect of yet another EP_2 antagonist (ZKxxxx888) in combination with rofecoxib is disclosed. It is clear from the data in the Exhibit that the molecules of the present invention are useful in reducing the number of

ovulated oocytes *in vivo*. Given this amount of detailed experimental evidence, the Office Action has not established why one of ordinary skill in the art would doubt that other representative molecules of the claimed genus would also be useful towards the claimed end uses. As such, the rejection is without scientific merit.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine with in the art. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 1–18 are rejected under §103(a) as allegedly being rendered obvious by the teachings of Breyer (*Annals of NY Academy of Sciences*, 2000) in view of Narumiya (*Physiological Reviews*, 1999), Hizaki (*PNAS*, 1999), Norel (*BJP*, 1999) further in view of Norel (*British Journal of Pharmacology*, 1999) and Noble (*American Family Physician*, 2000). This rejection is respectfully traversed.

The basis for the obviousness rejection can be found in the paragraphs bridging pages 9 and 10 of the outstanding Office Action. Therein it is alleged that:

> Breyer et al. teaches the disruption of EP2 receptors and inhibition of COX-2 can inhibit the ovulation (Examiner notes: oocyte maturation), fertilization and implantation (See page 228 – 229).
>
> Hizaki et al. also teaches the lacking of EP2 receptor in mice may lead to abortive expansion of the cumulus and impaired ovulation (See particularly the abstract and page 10502 – 10505 Results Section).
>
> Nirumiya et al. teaches a general review of EP receptors. Specifically, Nirumiya et al. teaches that the relationship between PGE2 and EP2 receptors in a way that PGE2 interacts with EP2 causing increase in cAMP which in result would induce oophorus maturation (See page 1217, Reproduction section).
>
> Norel teaches AH6809 as a EP1/EP2 antagonists (See the abstract).
>
> Noble et al. teaches celecoxib as a COX-2 inhibitor (See the abstract).
>
> It would have been obvious to one of ordinary skill in the art at the time of invention to employ AH6809 andr Celecoxib in a method of controlling fertility or impairing cumulus expansion and oocyte maturation.

It is respectfully submitted that methods of the instant invention comprise use of molecules that have different biological targets and, as such, the combined effect thereof could not have been expected by one of ordinary skill in the art. Thus, the compounds of each reference are not taught for the same specific purpose. For example, compounds of Norel are directed to the antagonism of EP1/EP2 receptor whereas the compounds of Noble are directed to inhibition of Cox-2. The cited teachings of the Breyer, Hizaki, and Narumiya, even at the broadest interpretation, do not teach or suggest a combination of EP2 antagonism and Cox-2 inhibition. Absent hindsight, nothing in the teachings of any of the cited references would guide or sufficiently motivate a skilled artisan to reformulate the references in a manner and/or form taught by the instant invention. Obviousness requires a suggestion of all the elements in a claim (*CFMT Inc., v Yieldup Int'l Corp.* 349 F.3d 1333, 1342 [68 USPQ2d 1940] (Fed. Cir. 2003)) and requires a reason that would have prompted [a skilled worker] to combine the elements in the way the claimed new invention does. *Ex parte Karoleen B. Alexander*, Appeal No. 2007-2693; decided: November 30, 2007 (86 USPQ2d 1120). Applicants respectfully submit that a combination of the cited references, even at their broadest interpretation, fails to teach or suggest the elements of Appellants' claims and provide a reason that would have prompted the skilled worker to reformulate the elements to arrive at the present claims. As such, the rejection is without legal merit.

With respect to Applicant's rebuttal of *prima facie* case of obviousness by relying on unexpected properties of the claimed combination, the Examiner now alleges that the "unexpected benefits must be of a scope reasonably commensurate with the scope of the subject matter claimed." See, page 11 of the Office Action. In view of the experimental data submitted herewith in the Exhibit, relief from this rejection is respectfully requested. The experimental data enclosed herewith provides *additional* corroborating scientific evidence (other than what was provided in Dr. Lindenthal's declaration under §1.132) that the claimed combination of EP_2 antagonists and Cox-2 inhibitors is unobvious over the cited art references.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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